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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/582,711	06/30/2000	Guy Serre	045636-5037	8393

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MORGAN LEWIS & BOCKIUS LLP
1111 PENNSYLVANIA AVENUE NW
WASHINGTON, DC 20004

EXAMINER
COOK, LISA V

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1641	19

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/582,711	Applicant(s) SERRE ET AL.	
	Examiner Lisa V. Cook	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7 and 9-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7 and 9-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group B (claims 1, 5, 9, 10, and 13) drawn to compositions comprising X1-Ser-Cit-His-X2 in Paper No.18, filed 10/7/02 is acknowledged. The traversal on the ground(s) "that the peptides in the instant application all comprise the citrullinated tripeptide Ser-Cit-His therein the Ser-Cit-His is a common technical feature linking together all of the instantly claimed inventions. The claims no longer site peptides sequence identification 3, 5, and 6. This argument was carefully considered and found convincing. The restriction requirement is vacated.

2. Currently, claims 1, 3, 5-7, and 9-15 with respect to citrullinated tripeptide Ser-Cit-His are pending and under examination.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 6 remains rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. There are no claimed steps reciting the washing or removal of unbound materials. If no separation will be performed it is unclear how the complex will be identified from the reaction solution containing both bound ad unbound material.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 6 remains rejected under 35 U.S.C. 112, first paragraph, as based on a disclosure which is not enabling. The method has insufficient steps. These critical or essential to the practice of the invention, but not included in the claim(s) is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976). Merely, reciting the use of reagents in an assay format is not considered a proper method step.

An assay as recited in the preambles of claim 6, requires at least a contact step between reagent and sample – resulting in binding/complex formation, separation, detection, and a correlation step directed to the analysis of interest. The recited claims do not include the required steps for contact, detection, and correlation. Appropriate correction required.

Response to Argument

5. Claim 6 has been amended to recite the removal of the rest of the biological sample after antigen/antibody complex formation. However this remains unclear because it is not known if the entire biological sample will be removed (bound and unbound materials) or only the unbound biological sample. Therein the rejections recited above are maintained. It is suggested that the claims recite bound biological sample and unbound biological sample for clarity and obviate the rejection.

NEW GROUNDS OF REJECTION

Claim Objections

6. Claims 6 and 13-15 are objected to because of the following informalities:

I. In claim 6, "at" appears to be missing in line 3. The line reads with least one antigen.

II. Claims 13-15 are objected to under 37 CFR 1.821(d) for failing to recite the SEQ ID NOS. in the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 1, 5, 9-10 and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claim 1 is directed to a peptide comprising a tripeptide motif Ser-Cit-His recognized by anti-flaggrin autoantibodies. However, applicants intended meaning with respect to this limitation is not clear. Since citrulline is an amino acid and not a peptide, the meaning of the expression "tripeptide" is not clear. Please explain.

B. Claims 5, 6, 7, 9, 10, and 12 recite the limitation "at least one antigen" in claim 1. There is insufficient antecedent basis for this limitation in the claim. Claim 1 merely reads on a peptide. Appropriate correction is required.

C. Regarding claims 6, 7, and 12, the phrase "any suitable means", "as well as", and "suitable buffers" render the claims indefinite because it is unclear what limitations are intended. As recited no clear identification with respect to what these limitations are set forth by the claims or the disclosure. As recited the metes and bounds of the claims cannot be determined. See MPEP § 2173.05(d).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 1, 3, 5-7, and 9-15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description in this case only sets forth SEQ ID NO: 3, 5, and 6, and equivalent degenerative codon sequences thereof and therefore the written description is not commensurate in scope with a peptide molecule comprising the particular tripeptide motif's Ser-Cit-His as recited in claims 1 and 13-15.

The language of claims 1, 13, 14, and 15 are directed to peptides comprising the motif Ser-Cit-His however no such embodiment it demonstrated in the instant application. The sequence identified in the application are directed to known sequences, however not one sequence comprising the motif Ser-Cit-His is identified or shown to be possessed by applicant. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Thomas E. Creighton, in his book, "Proteins: Structures and Molecular Properties, 1984, (pages 314-315) teaches that variation of the primary structure of a protein can result in an instable molecule. He also teaches a single amino acid change can cause a mutant.

Thus, the structure of the peptide of claims 1 and 13-15 are not disclosed. With the exception of SEQ ID NO:3, 5, and 6 (which do not include the cit- amino acid), the skilled artisan cannot envision the detailed structure of the encompassed compositions and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and a reference to a potential method of isolating it. The nucleic acid itself is required. See *Fiers v. Revel*, 25 USPQ 2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016.

Furthermore, In *The Reagents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids/peptides by only their functional activity does not provide an adequate written description of the genus. The court indicated that while Applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus.

At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention". Further the disclosed sequences do not comprise the tripeptide motif and as such do not appear to encompass the instant invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 1, 5, 9-10 and 13-15 are directed to non-statutory subject matter. The invention as claimed reads on any peptide comprising Ser-Cit-His including antigenic compositions, where the compositions include naturally occurring as well as synthetic compositions. Nonnaturally occurring compositions are considered to be patentable subject matter with in the scope of 35 U.S.C. 101, but products occurring in nature are considered non-statutory and non-patentable. See Official Gazette, 1077 O.G. 24, April 21, 1987. It is recommended that the claims incorporate the claim language, "isolated" or "purified" to overcome this rejection.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claims 1, 3, 5-7, and 9-15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schellekens et al. (Arthritis and Rheumatism, Volumn 40, No 9, Suppl 08, November 8, 1997, Abstract), in view of

The invention relates to a flaggrin unit sequence comprising many X-Arg-Y units and in particular the Ser-Arg-His unit present on at least one of the sequences SEQ ID no. 3, 5, and 7. "This work resulted in the production of artificial antigens, which are recognized specifically by AFAs present in the serum from RA patients, and which consist of recombinant or synthetic polypeptides derived from the sequence of filaggrin or from portions of it, by substituting at least one arginine residue with a citrulline residue."

On page 4, lines 24-38 of the specification applicant discloses the inventive concept in application FR 96/10651 filed 30 August 1996 in the name Biomerieux. This invention directed to the modification/substitution of arginine residues to citrulline in peptides therein producing epitopes recognized by autoantibodies in sera from rheumatoid arthritis patients is disclosed by Schellekens. See abstract.

Schellekens et al. does not specifically reciting the tripeptide motif Ser-Cit-His. More specifically Schellekens et al. do not teach what peptides exist on either side of the Arg converted to Cit.

It stands to reason that the peptides of Schellekens et al. exhibiting the detection capability as the instant peptides (measuring autoantibodies in sera from RA patients) includes the Ser-Arg-His motif although not specifically recited. Not only the specific teachings but also the inferences which one skilled in the art would reasonably be expected to draw from a reference should be taken into account. In re Preda (CCPA 1968) 401 F2d 825, 159 USPQ 342.

Therein it would have been obvious to one of ordinary skill in the art to take known peptide sequences and modify the peptides via citrulilination procedures involving the specific conversion of an arginine residue to citrulline as taught by Schellekens et al. in order to produce peptides of the instant invention capable of measuring autoantibodies in sera from RA patients as a means for finding and optimizing the specific peptides of interest. Because Schellekens et al. taught that the arginine residue conversion to citrulline was the key peptide modification. With respect to the peptides on either end of that conversions such differences are considered mere routine optimization with respect to the initial peptides utilized. Absent evidence to the contrary the teaching of Schellekens et al. encompass the instant invention.

Schellekens et al. differs from the instant invention in not teaching anti-flaggrin autoantibodies present in rheumatoid arthritis patients.

However, Serre et al. teach methods and kits to diagnosis rheumatoid arthritis via the contacting of an antigen to a biological sample to form an immune complex with autoantibodies as an indicator of RA. See claim 1 and 2, abstract, and column 1, lines 39-52.

It would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to take the peptide "Cit"compositions as taught by Schellekens et al. and format them into human filaggrin antigens (anti-flaggrin autoantibodies) to measure RA in methods and kit as in patent #5,888,833 of Serre et al. because Serre et al. taught that precise antigen identification and purification was operable (column 1, lines 59-60). The antigens directed to flaggrin were particularly useful in RA measurements. Column 10, lines 1-32.

One having ordinary skill in the art would have been motivated to use the citrulline peptide compositions to detect RA because Schellekens et al. taught that antibodies directed towards the citrullinated peptides could be detected in 76% of RA sera with a specificity of 95% against disease controls. See abstract.

16. For reasons aforementioned, no claims are allowed.

17. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 308-4242, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (703) 305-0808. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (703) 305-3399.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Lisa V. Cook
CM1-7B17
(703) 305-0808
12/19/02

LONG V. LE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600
12/30/02